II. REMARKS

Preliminary Remarks:

Amendment of the claims

Claims 20, 29, 55, 68, 80, 81, and 85 are amended, and claims 56, 57, 69, 70, 82, and 83 are canceled. Claims 20, 29, 38-40, 55, 62, 63, 68, and 75-81 and 84-92 are currently pending.

Independent claims 20, 29, 80, and 85 are amended to expressly specify that the tetravalent antibody dimer has four antigen-binding sites that bind specifically to TAG-72, as described in Example 4 on pages 51-52.

Independent claims 20, 29, 80, and 85 are further amended to specify that a C_H2 domain is deleted from, and a C_H3 domain is fused directly to the hinge region of, each of the four antibody heavy chain polypeptides in the dimeric antibody.

Claims 55, 68, and 81 are amended by deleting reference to the antibodies as being "chimeric."

Patentability Remarks:

35 U.S.C. §112, second paragraph

(A) Claims 20, 29, 38-40, 55, 62, 63, 68, and 75-81, and 84-92 are rejected under 35 U.S.C. §112, second paragraph, because it is allegedly unclear whether the tetravalent antibody dimer of the claimed invention has two or four antigen-binding sites.

The applicants do not agree that the claims are indefinite, because one of skill in the art would understand from the language of independent claims 20, 29, 80, and 85 that the tetravalent antibody dimer of the claimed invention has four antigen-binding sites. Independent claims 20, 29, 80, and 85 use similar language to describe the tetravalent antibody dimer of the claimed invention. For example, claim 20 describes the tetravalent antibody dimer of the claimed invention as follows:

> "...a dimeric antibody that binds specifically to TAG-72 ...which dimeric antibody comprises two antibodies that are non-covalently associated to form a tetravalent antibody dimer,
>
> wherein each of the antibodies in the dimer comprises two antibody heavy chain polypeptides having the heavy chain variable region amino acid sequence shown in Figure 4A (SEQ ID NO: 7), and two antibody light chain polypeptides having the light chain variable region amino acid sequence shown in Figure 5A (SEQ ID NO: 9), and has two antigen-binding sites that bind specifically to TAG-72; and

wherein a C_H2 domain is deleted from each of the four antibody heavy chain polypeptides in the dimeric antibody..."

From the description of the tetravalent antibody dimer provided by claim 20 and the other independent claims, it is clear that the tetravalent antibody dimer comprises two non-covalently associated antibodies, each of which comprises two antibody heavy chain polypeptides and two antibody light chain polypeptides and has two antigen-binding sites that bind specifically to TAG-72. Therefore, the tetravalent antibody dimer of the claimed invention clearly has four antigen-binding sites. Nonetheless, in order to expedite prosecution, independent claims 20, 29, 80, and 85 are amended to expressly describe the tetravalent antibody dimer of the claimed invention as having four antigen-binding sites. Accordingly, withdrawal of the rejection of the claims under 35 U.S.C. §112, second paragraph, for alleged indefiniteness with regard to the number of antigen-binding sites on the tetravalent antibody dimer is respectfully requested.

(B) Claims 55, 68, and 81 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite in the reference in the claims to the antibodies of the claimed invention as being "chimeric" antibodies.

Claims 55, 68, and 81 are amended by deleting the reference to the antibodies of the claimed invention as being "chimeric" antibodies. Withdrawal of the rejection of claims 55, 68, and 81 under 35 U.S.C. §112, second paragraph, for alleged indefiniteness with regard to the use of the term "chimeric" is respectfully requested.

35 U.S.C. §112, first paragraph

Claims 20, 29, 38-40, 55, 62, 63, 68, and 75-81, and 84-92 are rejected under 35 U.S.C. §112, first paragraph, because the specification is considered to enable one of skill in the art to make and use the claimed invention wherein the C_H2 domain is deleted or the C_H3 domain is fused directly to the hinge region in the heavy chains of the tetravalent antibody dimer, but allegedly does not enable the invention wherein the C_H2 domain is deleted and replaced with an amino acid spacer. In support of the rejection, the official action refers to experimental results described in the specification and in published references which show that antibodies in which the C_H2 domain is deleted and replaced by an 10-residue glycine-serine spacer do not associate non-covalently to form a tetravalent antibody dimer.

Independent claims 20, 29, 80, and 85 are amended to specify that a C_H2 domain is deleted from, and a C_H3 domain is fused directly to the hinge region of each of the four antibody heavy chain polypeptides in the dimeric antibody, in order to expedite prosecution. The applicants respectfully submit that undue experimentation would not have been required for one of skill in the art to prepare C_H2 domain-deleted antibodies according to the claimed invention

with amino acid spacers having different lengths and amino acid compositions, and identify spacers that can be inserted in place of a deleted C_H2 domain in antibodies of the claimed invention that operate successfully as described by the specification. Accordingly, the applicants reserve the right to file one or more divisional applications with claims directed to embodiments of the disclosed invention wherein a C_H2 domain is wholly or partially deleted and replaced with an amino acid spacer as described in the specification. Withdrawal of the rejection of claims 20, 29, 38-40, 55, 62, 63, 68, and 75-81, and 84-92 under 35 U.S.C. §112, first paragraph, is respectfully requested.

35 U.S.C. §§103(a)

(A) Claims 20, 29, 38-40, 63, 76-80, and 84-92 are rejected under 35 U.S.C. §103(a) as being obvious in view of Beresford *et al.* (1999, International J. of Cancer, 81(6):911-917), further in view of Kashmiri *et al.* (5/11/2000, WO 00/26394), Anderson *et al.* (U.S. Patent No. 6,348,581 B1) and Thorpe *et al.* (U.S. Patent No. 6,342,219 B1).

Beresford *et al.* describes a divalent, single chain Fv protein [$sc(Fv)_2$] that comprises two CC49 light chain and two CC49 heavy chain variable regions connected by linker polypeptides.

Kashmiri *et al.* is cited as disclosing the amino acid sequences of the V_H and V_L regions of humanized CC49 antibody shown in Figures 4A and 5A.

Anderson *et al.* is cited as suggesting the use of humanized CC49 antibodies, including such antibodies that are conjugated to cytotoxic agents.

Thorpe *et al.* is cited as teaching the use of antibodies conjugated to cytotoxins and other biologically active moieties for cancer therapy.

To establish a *prima facie* case of obviousness, the examiner must show that the prior art references themselves or the knowledge generally available to one of ordinary skill in the art would (1) provide some suggestion or motivation to modify or combine reference teachings to obtain the claimed invention, (2) teach or suggest all of the claim limitations, and (3) provide a reasonable expectation that the claimed invention can be made or used successfully. *In re* Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). *See* M.P.E.P. § 2142.

In determining if there is obviousness in the first instance, "it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." *In re* Linter, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972). Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or

motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). *See* M.P.E.P. § 2142.

Beresford *et al.* describes a divalent, single chain Fv protein construct that comprises two CC49 antibody light chain variable regions (V_L) and two CC49 heavy chain variable regions (V_H) connected by linker polypeptides (L), which has the structure "V_L-L-V_H-L-V_L-L-V_H" (see page 911, right column). Although the sc(Fv)$_2$ structure formed by association of the linked CC49 light and heavy chain variable regions is referred to by Beresford *et al.* as a "dimer," the sc(Fv)$_2$ "dimer" described by Beresford *et al.* has only two antigen-binding sites. The present application defines an antibody "dimer" of the claimed invention as a complex formed by the non-covalent association of two antibodies, each of which comprises two heavy chains and two light chains which combine to form two antigen binding sites. In contrast to the sc(Fv)$_2$ "dimer" described by Beresford *et al.*, an antibody dimer according to the present invention comprises four heavy chains and four light chains (H_4L_4), and has four antigen-binding sites (*i.e.*, is tetravalent).

In the statement of the rejection, the examiner incorrectly characterized the CC49 sc(Fv)$_2$ dimer described by Beresford *et al.* as one in which "two divalent antibodies non-covalently associate ...." (see page 8 of the official action, mid-page). As can be seen from the chromatographic data in Fig. 2 of Beresford et al. (page 913), the divalent CC49 sc(Fv)$_2$ dimers do not associate non-covalently to form tetravalent (H_4L_4) complexes. Beresford et al. expressly teaches that sc(Fv)$_2$ and (scFv)$_2$ dimers both elute from size exclusion chromatography as single peaks of approximately 60 kDa, "with no evidence of aggregates or monomeric scFv" (*see* the caption to Fig. 2). In view of the foregoing, it is clear that Beresford *et al.*, in combination with Kashmiri et al., Anderson et al., and Thorpe et al., neither described nor suggested the dimeric, tetravalent CH2 domain-deleted anti-TAG72 antibody of the claimed invention to one of ordinary skill in the art. The applicants therefore respectfully request that the rejection of claims 20, 29, 38-40, 63, 76-80, and 84-92 under 35 U.S.C. § 103(a) as having been obvious in view Beresford *et al.* in combination with the cited secondary references be withdrawn.

(B) Claims 20, 29, 38-40, 55, 62-63, 68, 75-81, and 84-92 are rejected under 35 U.S.C. §103(a) as being obvious in view of Gillies et al. (1990, Human Antibodies and Hybridomas, 1(1):47-54), as evidenced by the specification, in view of Kashmiri et al. (5/11/2000, WO 00/26394), Anderson et al. (U.S. Patent No. 6,348,581 B1) and Thorpe et al. (U.S. Patent No. 6,342,219 B1).

Gillies *et al.* describes chimeric antibodies ch14.18 and B72.3 in which the CH2 domains are deleted and the CH3 domain is fused directly to the hinge region. Antibody ch14.18 binds to disialoganglioside G_{D2} (present on neuroblastoma cells), and antibody B72.3 binds to TAG-72 (with lower affinity than CC49). The relevance of the secondary references, Kashmiri et al., Anderson et al., and Thorpe et al., is discussed above. The examiner alleges that it would have been obvious to modify the teachings of Gillies *et al.* in view of the cited secondary references to obtain the dimeric, tetravalent, C_H2 domain-deleted, anti-TAG-72 antibodies of the claimed invention. The examiner points to the applicants' specification as evidence that CH2 domain-deleted antibodies in which the CH3 domain is fused directly to the hinge region are inherently capable of associating non-covalently to form tetravalent (H_4L_4) complexes such as those of the claimed invention.

As stated above, to establish a *prima facie* case of obviousness, the examiner must show that the prior art references themselves or the knowledge generally available to one of ordinary skill in the art would (1) provide some suggestion or motivation to modify or combine reference teachings to obtain the claimed invention, (2) teach or suggest all of the claim limitations, and (3) provide a reasonable expectation that the claimed invention can be made or used successfully. *In re* Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). *See* M.P.E.P. § 2142.

The prior art can be modified or combined to reject claims as prima facie obvious as long as there is a reasonable expectation of success. *In re* Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Obviousness does not require absolute predictability, however, at least some degree of predictability is required. *In re* Rinehart, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure." *In re* Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

"A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue." In re Corkill, 711 F.2d 1496, 226 USPQ 1005 (Fed. Cir. 1985). A demonstration that a claimed compound has unexpected advantageous properties is objective evidence of nonobviousness. *See* In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963).

The applicants respectfully submit that claimed invention would not have been obvious to one of ordinary skill in the art in view of the cited references. The examiner relies on the disclosure of the claimed invention in the specification as evidence that non-covalent association is an inherent property of C_H2 domain-deleted antibodies in which the C_H3 domain is fused directly to the hinge region. However, this reliance is misplaced and, as discussed

below, is incorrect. It is established that extrinsic evidence may be offered to show that a reference anticipates a claimed invention. "Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991) (See the discussion of inherent anticipation under 35 U.S.C. § 102 in the Manual of Patent Examining Procedure, § 2131.01). The examiner's reliance on the applicants' specification to show that the claimed invention's unpredicted properties are inherent to the claimed invention is improper because (a) the applicants' specification is not extrinsic evidence, and (b) one of ordinary skill in the art would not have recognized that non-covalent association is necessarily an inherent property of C_H2 domain-deleted antibodies in which the C_H3 domain is fused directly to the hinge region.

The dimeric antibody of the claimed invention comprises two C_H2 domain-deleted, anti-TAG-72 antibodies in which the C_H3 domain is fused directly to the hinge region, which antibodies non-covalently associate to form a significant amount of tetravalent antibody dimer having four antigen-binding sites that bind specifically to TAG-72. As described in Example 4 of the specification, the dimeric, tetravalent, C_H2 domain-deleted, anti-TAG-72 antibodies of the claimed invention constitute approximately 45-50% of the antibodies in a mixture of the antibody light and heavy chains, and are purified by size-exclusion chromatography as a discrete peak that indicates conformational uniformity (*see* Figure 9).

The dimeric, tetravalent, C_H2 domain-deleted, CC49-derived antibodies of the claimed invention have significantly greater binding activity than monomeric, divalent, C_H2 domain-deleted antibodies having the same CC49-derived antigen-binding sites. As described in Example 7, dimeric, tetravalent, C_H2 domain-deleted, CC49-derived antibodies of the claimed invention bind to TAG-72 with an estimated Kd of 0.15nM, whereas monomeric, divalent, C_H2 domain-deleted antibodies having the same CC49-derived antigen-binding sites bind to TAG-72 with an estimated Kd of 2.4 nM, a 15-fold difference (*see* Figure 11A).

These properties of C_H2 domain-deleted antibodies were not described or suggested by Gillies et al. or any of the cited secondary references, and would not have been expected by one of ordinary skill in the art at the time the invention was made. Gillies et al. teaches that when C_H2 domain-deleted antibodies produced by mixing C_H2 domain-deleted heavy chains with unmodified light chains are separated by size-exclusion chromatography, monomeric 120 KDa antibodies (H_2L_2) and 60 KDa half-antibodies (HL) migrate as a single peak (*see* page 50, left column). Gillies et al. also refer to the work of Morrison et al. (Ann. NY Acad. Sci., 1987, 507:187, cited by Gillies et al. as ref. 3), which they describe as showing that antibody light chains and C_H2 domain-deleted heavy chains encoded by a human C3 gene form only fully assembled, covalently bound, divalent H_2L_2 antibodies (*see* page 50, left column). One of ordinary skill in the art would reasonably expect that the presence of significant amounts of

dimeric, tetravalent 240 KDa antibodies (H_4L_4) in the antibody mixtures analyzed Gillies et al. and Morrison et al. would have been detected; however, Gillies et al. does not mention that dimeric, tetravalent 240 KDa antibodies (H_4L_4) were observed. One of ordinary skill in the art would therefore reasonably conclude that the C_H2 domain-deleted antibodies described by Gillies et al. do not form a significant amount of dimeric, tetravalent 240 KDa antibodies (H_4L_4).

The successful production of the dimeric, tetravalent, C_H2 domain-deleted, anti-TAG-72 antibodies of the claimed invention, and their significantly enhanced affinity relative to monomeric, divalent anti-TAG-72 antibodies was an unexpected result that was not described or suggested by Gillies et al., in combination with Kashmiri et al., Anderson et al., and Thorpe et al., and could not have been predicted by one of ordinary skill in the art at the time the invention was made. Accordingly, the claimed invention would not have been obvious to one of ordinary skill in the art in view of the cited references, and withdrawal of the rejection of claims 20, 29, 38-40, 55, 62-63, 68, 75-81, and 84-92 under 35 U.S.C. § 103(a) in view of the cited references is respectfully requested.

III. IN CONCLUSION

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If the examiner identifies any points that he feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Please charge any fees or credit any overpayments associated with the submission of this response to Deposit Account Number 03-3975.

Respectfully submitted,

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